Peer Review File

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Reviewer A

Comment A-1-1:

I am somehow confused with the objectives of this manuscript. The title suggests a general review but the paper sketch shows data obtained from the Japanese hemovigilance systems, which are dual. In general, the style is wordy and many repeats should be avoided.

Reply A-1-1: According to the comment, the title was changed as "Incidence and severity of adverse effects related to platelet transfusion: A narrative review of the literature and the recent hemovigilance data of Japan". Additionally, repeated information in the main text has been corrected.

Changes in the text: Pages 4-36

This change was applied to the title, abstract and all the text in the revised manuscript (change in red).

Comment A-1-2:

I would have been interested in knowing once for all at the beginning of the manuscript how the platelet transfusion bags are processed in Japan; instead, manufacturing and processing appeared as scattered paragraphs in diverse occasions. What are the characteristics of the Japanese PCs? Collection, manufacturing, filtration and time to filtration, volume and dos (never said), use of PAS (and which?), use or PRT (and which? or BD, and which?), ABO identity/compatibility/occasional mismatch, HLA compatibilité, HPA? (no mention), etc. And how this practice differs from other large HV systems, the British, French, Dutch etc, to cite the 3 most comprehensive (or the FDA).

Reply A-1-2: Thank you very much for the helpful comment. In the revised

manuscript, we have described the characteristics of the Japanese PCs as an independent section subtitled as “Production and supply of platelet concentrates in Japan” (formerly as section 2-2).

Changes in the text: Pages 10-12 / Lines 148-188

Production and supply of platelet concentrates in Japan

The Japanese Red Cross Society (JRCS), as a sole operator of blood services, controls blood collection, processing and supply of blood products nationwide (38,39). In Japan, all PCs transfused are leucoreduced single-donor apheresis platelets. Of 4,707,951 voluntary non-remunerated donations in 2018, platelet apheresis donations accounted for 620,414 (13.2%), and 808,179 PC bags were distributed nationwide (40,41).

Eligibility criteria for platelet apheresis donation are as follows: age of 18 to 69 for male, 18 to 54 for female, body weight of 45 kg or more for male and 40 kg or more for female, hemoglobin level of 12 g/dL or more, and platelet count from 0.15 to 0.6 million/μL. After donor’s skin disinfection with 10% povidone-iodine followed by 70% isopropyl alcohol and the diversion of the initial 25 mL portion of blood, up to 600 mL of platelets suspended in plasma can be collected by any of three collection systems: CCS (Haemonetics), Terusys-S (Terumo), and Trima (Terumo) (36,39). More than 0.2, 0.4, 1.0, 2.0, 3.0, 4.0 x 1011 platelets are contained in 1-, 2-, 5-, 10-, 15-, 20-unit PC bags respectively, and 10-unit PC bags (volume of about 200 mL) are the most commonly used in clinical practice (35). All PCs are leukoreduced before storage, stored at 20 to 24°C with agitation, and visually inspected for the presence of aggregates and/or swirling before issue (36).

ABO-identical, single-donor apheresis platelets are routinely supplied by the JRCS, however, human leukocyte antigen (HLA) and human platelet antigen (HPA) matching is given priority over ABO compatibility when there is a need for HLA- or HPA-matched platelets. Currently, approximately 70% of supplied HLA-matched platelets are ABO-identical. Non–ABO-identical HLA- or HPA-matched platelets with high ABO antibody titers (>1:128) are administered at the physician’s discretion (42).

The JRCS has already implemented universal leukoreduction and initial flow diversion, but not bacterial culture screening or PRTs so far (36). For reducing

clinically relevant risk of sepsis due to TTBIs, the shelf-life of PC is presently limited to 3 days. This is the shortest when compared to other developed countries (22,29,43–45), where bacterial screening of PC bags and/or PRTs are being implemented as strategies to mitigate TTBIs (Table 1). This "3-day limitation policy" has contributed to the low incidence of fatal TTBI related to platelet transfusion in Japan, which is currently estimated to be 0.1 in one million PC bags (36).

Reflecting effectiveness of decreasing the volume of plasma for preventing ATRs, which contains inflammatory cytokines and protein components (46–48), the JRCS started to provide washed PCs in 2016 (49). In contrast to Western countries, PAS-PCs, in which about 70% of plasma is replaced with platelet additive solution (PAS), are not available so far in Japan.

Comment A-1-3:

In the next development of adverse reactions, there is a mix of citations of mitigations measures, but it is unclear to know whether this is general practice or a Japanese practice (references are often outside Japan).

Reply A-1-3: We apologize for the unclarity of the first manuscript. For improving the readability, in each section of each adverse event, information about Japanese situation has been placed after general instructions.

Changes in the text: Pages 17-34 / Lines 278-585
This change was applied to the related text in the revised manuscript.

Comment A-2:

In aggregate, 2 points are missing which should have been of utmost relevance

(1) An inside comparison of the 2 Japanese reporting systems, and an outside comparison with other reference systems; this may affect the reported incidence of each type of adverse reaction

Reply A-2: Thank you for the comment. As for the inside comparison of the 2 Japanese reporting systems, we have already described the difference in the first manuscript: paper-based reporting in JRCS system versus online reporting in NIID

system. The point is that reporting to these two systems are not mandatory. To clearly compare the difference of reporting system outside Japan, we have added the related information in the main text as shown below. The point about an outside comparison with other reference systems raised by the reviewer has been added in Limitation section.

Changes in the text:

Two existing hemovigilance systems; Page 13 / Lines 212-218

The hemovigilance situations on monitoring adverse events to blood transfusion vary from country to country. It is mandatory to report fatal cases in the US (52), serious or unexpected adverse reactions in Canada (44), serious adverse reactions and events in the UK and Belgium (53,54), any suspected transfusion reactions in France and Switzerland (55,56). On the other hand, in Australia and New Zealand, reporting of serious adverse reactions is performed on a voluntary basis, as is in Japan (45,57).

Limitation and future perspective; Page 34 / Lines 588-590

This article has several limitations. First, the incidence of each type of adverse reaction, referred from the literatures outside Japan, might be affected by the inter-country difference of reporting system.

Comment A-3:

(2) A critical presentation of adverse events reported to mitigation measures: for example, FHTRs maybe strikingly different if supernatant is 2/3 PAS and 1/3 plasma or 3/3 plasma. Accumulation of cytokines in 3d PCs should be different from that of 5 to 7 d PCs What in Japan, with a 3d P˙C policy, affords a reduction of Ans seen in countries having no PAQ, apheresis platelets only, no PRT, swift leukoreduction (<10^6 I presume?), ABO compatibility???

Reply A-3: Thank you for the comment. Information about type of platelet component (pooled, apheresis-derived, leukoreduced etc.) used in each study has been added in the related sentences of the main text. Moreover, the characteristics of the Japanese PCs including “3-day limitation policy” for platelet storage as an independent section subtitled as “Production and supply of platelet concentrates in Japan” (formerly as

section 2-2). Please refer to the Reply A-1-2.

Changes in the text: Pages 17-34 / Lines 278-585
This change was applied to the related text in the revised manuscript (change in red).

Comment A-4:
It is suggested to redraft the manuscript in order to provide benchmarks analysis to international readership and alter the title accordingly.

Reply A-4: According to the comment, we have revised the title and the main text as to improve the readability.

Changes in the text: Pages 1, 4-37
This change was applied to the title, the abstract and all the text in the revised manuscript (change in red).

Reviewer B

The authors made use of the two sources of Japan haemovigilance system to describe on the adverse events of platelet transfusion. Despite that there might be overlapping or under- reporting, the data in this review article is interesting. However, there are a few area to address:

Comment B-1. Consider to revise the title of the manuscript to include geographic information e.g. in Japan

Reply B-1: Thank you for the comment. The title has been revised as “Incidence and severity of adverse effects related to platelet transfusion: A narrative review of the literature and the recent hemovigilance data of Japan”.

Changes in the text:

Title; Page 1 / Lines 1-3

Incidence and severity of adverse effects related to platelet transfusion:
A narrative review of the literature and the recent hemovigilance data of Japan

Comment B-2. Some descriptions of the patients' characteristics of platelet transfusion.

Reply B-2: According to the comment, the patients' characteristics of platelet transfusion have been added in the Introduction section as shown below.

Changes in the text:

Introduction; Page 4 / Lines 76-82

In clinical practice, platelet transfusions are indicated for prevention or treatment of bleeding in patients with either low platelet counts or poor platelet function (1–3), the majority of which comprise of prophylactic transfusion for patients with chemotherapy or hematopoietic progenitor cell transplantation to reduce the risk of spontaneous bleeding (4–7). Other cases, mostly in general medicine, cardiac surgery, intensive care unit etc., require therapeutic platelet transfusions for treating acute hemorrhage (6,7).

Comment B-3. In 2.2., needs to spell out clearly, diversion at collection and swirling at issue are implemented in Japan. Need to clearly state if bacterial culture and PRT are implemented as the second sentence in 2.2 is long and may be incorrectly punctuated. Besides, is there a use of PAS to reduce the plasm content?

Reply B-3: Thank you for the comment. In the revised manuscript, we have described the characteristics of the Japanese PCs as an independent section subtitled as “Production and supply of platelet concentrates in Japan” (formerly as section 2-2).

Changes in the text:

Production and supply of platelet concentrates in Japan; Pages 10-12 / Lines 149-188 (Please refer to Reply A-1-2).

Comment B-4. It appears that there was no mentioning of the current estimate of transfusion transmitted infection in Japan. It would be useful to compare with the reported incidence.

Reply B-4: According to the comment, we have added the estimate of TTBI and TTIs by HBV, HCV and HIV in the main text as shown below. Since the estimate can be affected by underreporting due to the nature of passive surveillance, the point has been added in Limitation section.

Changes in the text:

TTBI; Page 23 / Lines 393-395

From the hemovigilance data provided in Table 5, incidence of suspected and confirmed bacterial contamination is as low as 0.46 and 0.03 per 100,000 transfusion bags (including PC, RBC, and FFP).

TTI other than TTBI; Page 31 / Lines 539-543

In Japan, NAT testing of HIV, HBV and HCV was implemented in 1999, initially with a mini-pool of 500, then reduced to 50 in 2000, to 20 in 2004, and 10 years later, in 2014, the individual NAT was implemented. Recent estimated risk of HBV transmission is one in 2 million units, and those of HCV and HIV transmission are immeasurably small (35).

Limitations and future perspective; Page 34 / Lines 590-595

Second, the difference of reporting systems and participants might limit the direct comparison of the two hemovigilance data of Japan. And underreporting might affect both collected data due to their nature of passive surveillance. Considering each advantage for collecting transfusion-related adverse events, integration of two hemovigilance systems seems reasonable.

Comment B-5:

As the authors decided the manuscript on adverse effects of platelet transfusion but also included adverse events following red cells and plasma transfusion, it

may be necessary to include some general comparisons in the manuscript.

Reply B-5: According to the comment, we have added general comparisons among platelet, RBC and plasma transfusions in the related sections in the abstract and the text.

Changes in the text:

Abstract; Page 4 / Lines 52-56

Among them, allergic and anaphylactic transfusion reactions, FNHTRs are frequent with platelet and plasma transfusions. Due to storage at room temperature, bacterial infections are more frequently caused by platelet transfusions than red blood cell or plasma transfusions.

ATRs & FNHTRs; Page 17 / Lines 279-281

ATRs and FNHTRs are frequent adverse reactions associated with platelet transfusions, and these incidences are reported to be higher than those associated with RBC or plasma transfusions (16,18,59,60).

TTBI; Page 20 / Lines 339-342

Platelets are stored at room temperature mostly due to negative impact of cold storage on platelet function and survival (82–84), which poses platelet components at a high risk of bacterial contamination compared to RBC and plasma component (31,36,85,86).

TRALI; Page 25 / Lines 421-427

Recipient risk factors for TRALI are liver transplantation surgery, chronic alcohol abuse, shock, higher peak airway pressure while being mechanically ventilated, current smoking, higher interleukin (IL)-8 levels and positive fluid balance, whereas blood component risk factors for TRALI are high-plasma-volume blood components, increased volume of transfused HLA class II antibody or anti-human neutrophil antigen (HNA) antibody (23,112–114).

TACO; Page 27 / Lines 461-463

TACO is the most frequent but underdiagnosed and underreported pulmonary complication of any blood component transfusion, including platelets (23,110,122).

HTR; Page 29 / Lines 501-502
As with the cases with TRALI, TACO, FNHTRs and ATRs, amounts of incompatible donor plasma in PC bags can cause hemolysis in recipients (23).